CORRESPONDENCE

Re: Loss of DNA Mismatch Repair: Effects on the Rate of Mutation to Drug Resistance

de las Alas et al. *(1)* recently reported that certain genes involved in the control of cellular sensitivity to etoposide may be more susceptible to mutation in cells lacking DNA mismatch repair (MMR) activity, with resulting resistance to the drug. They showed through clonogenic survival assays in MMR-deficient cell lines complemented with the MLH1 gene that sensitivity to etoposide was increased over that of the parental cell line, while the development of mutations affecting resistance was reduced.

Etoposide exerts its cytotoxic effect by inhibiting the nuclear enzyme topoisomerase II (topoII) *(2)*, of which there are two isoforms. TopoIIα and topoIIβ are the products of two different genes that have been mapped to chromosomes 17 and 3, respectively *(3,4)*. Studies have indicated that the degree of overall enzyme activity is an important factor in determining the activity of topoII inhibitors *(5)*. More specifically, the level of topoIIβ activity has been correlated to the sensitivity of breast cancer cell lines to etoposide *(6)*.

The method of de las Alas et al. involved transferring to the human colon cancer cell line HCT116 a wild-type copy of the MLH1 gene by complementing with chromosome 3 (designated NCT116/+chr3). In this case, such an approach is flawed in that complementing cells with chromosome 3 would also co-introduce another copy of the topoIIβ gene. Increased expression of topoIIβ from the newly introduced topoIIβ gene could itself increase the sensitivity of cells to etoposide as compared with control cells complemented with chromosome 2.

Complementing cells with an entire chromosome also introduces other genes that may directly or indirectly affect the sensitivity of cells to specific cytotoxic drugs.

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Response

The DNA mismatch repair (MMR)-deficient HCT116 cells were rendered repair proficient by transferring a copy of chromosome 3 containing a functional MLH1 allele, and Liu et al. point out that this would be expected to add an extra topoIIβ allele. If the topoIIβ level were a dominant determinant of etoposide (VP-16) sensitivity in these cells, then the extra allele would reasonably be expected to enhance VP-16 sensitivity and reduce the frequency of mutation to the resistant phenotype due to reduction in topoIIβ activity. However, there are several lines of evidence suggesting that topoIIβ is not a dominant determinant of VP-16 sensitivity and that the effects observed were, in fact, due to changes in MMR activity.

The most direct evidence is that a similar change in VP-16 sensitivity was observed in another pair of human cells that differ in MMR repair proficiency due to loss of MSH2 function. The deficient HEC59 cells have defects in both alleles of MSH2. When they were rendered repair proficient through the transfer of chromosome 2, which does not carry either a topoIIα or topoIIβ gene but does carry MSH2, they became 1.7-fold more sensitive to VP-16 *(1)*. Thus, despite the background of other genes on chromosome 2, the effect of MMR correction was detectable in this system as it was in the HCT-116 cells. In addition, as noted in our report, at the high concentrations of VP-16 used in the mutation rate studies, there was no significant difference in VP-16 sensitivity, indicating that if the topoII allele on chromosome 3 was functional, it had no effect on sensitivity at a cloning efficiency of 0.0002% *(2)*.

Other evidence derives from studies suggesting that topoIIα dominates over topoIIβ as a determinant of VP-16 sensitivity in whole cells, and that the 50% increase in topoIIβ that might have occurred with transfer of chromosome 3 would be expected to have a minimal effect on the mutation rate measurements that we made. First, yeast cells expressing only human topoIIβ were more sensitive to VP-16 than yeast cells expressing only human topoIIβ, indicating that the former was better at mediating the cytotoxic effects of VP-16 in the whole cell *(3)*. Also, up- or down-regulation of topoIIα levels produced large changes in VP-16 sensitivity consistent with this isoform being the dominant target *(4,5)*. In addition, cells selected with VP-16 and other topoII inhibitors have mutations in topoIIα [reviewed in *(6)*], but there are no reports of mutations in topoIIβ in VP-16 selected cells. In proliferating tissues, topoIIα levels appear to be substantially higher than topoIIβ levels and expression levels of topoIIβ in human cancer cell lines averaged 32 times higher than that of topoIIβ [reviewed in *(7)*].

Thus, although our available data do not exclude an effect of an extra topoIIβ allele, we believe that there is a reason-

able basis for considering that the change in MMR activity underlies the observed change in mutation rate.

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Re: Greying of America Will Foster New Strategies in Oncology

The Journal recently carried a News item *(1)* on the views concerning cancer in the aging population expressed by President Clinton's Cancer Panel. According to this Panel, the main treatment-related priority in the cancer therapy in an aging population is the requirement for individualization of the treatment and examination of the pharmacologic properties and toxicity of cancer drugs given to older patients. We would like to draw attention to one interesting and promising aspect of the interaction between some chemotherapeutics and statins in tumor therapy. The inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (the statins) inhibit synthesis of mevalonic acid, an essential precursor in cholesterol biosynthesis, and have commonly been used for the last several years to prevent and to treat atherosclerosis of the coronary vessels. Due to their ability to lower blood cholesterol levels, the statins presently are among the world's most commonly used drugs, especially in elderly patients. The mean age of patients receiving simvastatin in the Scandinavian Simvastatin Survival Study is 58.2 years for men and 60.5 years for women *(2)*.

However, the significance of statins' application may not be confined to the prevention and treatment of coronary heart disease. Lovastatin, which arrests cells in the G_1 phase of the cell cycle *(3)*, has been shown to exert antitumor effects in a variety of animal tumor models *(4,5)*. Results of phase I trials of lovastatin administered to cancer patients have also been reported *(6)*. Lovastatin will probably never be used successfully as a single antitumor agent. However, the interaction between statins and chemotherapeutics used for tumor treatment should be examined.

According to recent observations, statins could be able to increase antitumor activity of some other anticancer drugs. Lovastatin has already been shown to augment antitumor activity of cisplatin in a murine tumor model *(5)*, and simvastatin demonstrated synergistic antitumor effects when used with either BCNU (carmustine) or β-interferon *(7)*. Lovastatin was also demonstrated to target specifically drug-resistant P-glycoprotein-expressing tumor cells *(8)*, suggesting its possible application in the treatment of tumors refractory to chemotherapy.

In our recent study, we examined whether antitumor effects of doxorubicin may be potentiated *in vivo* by its combined use with lovastatin. Neither doxorubicin (at a dose of 5 mg/kg) nor

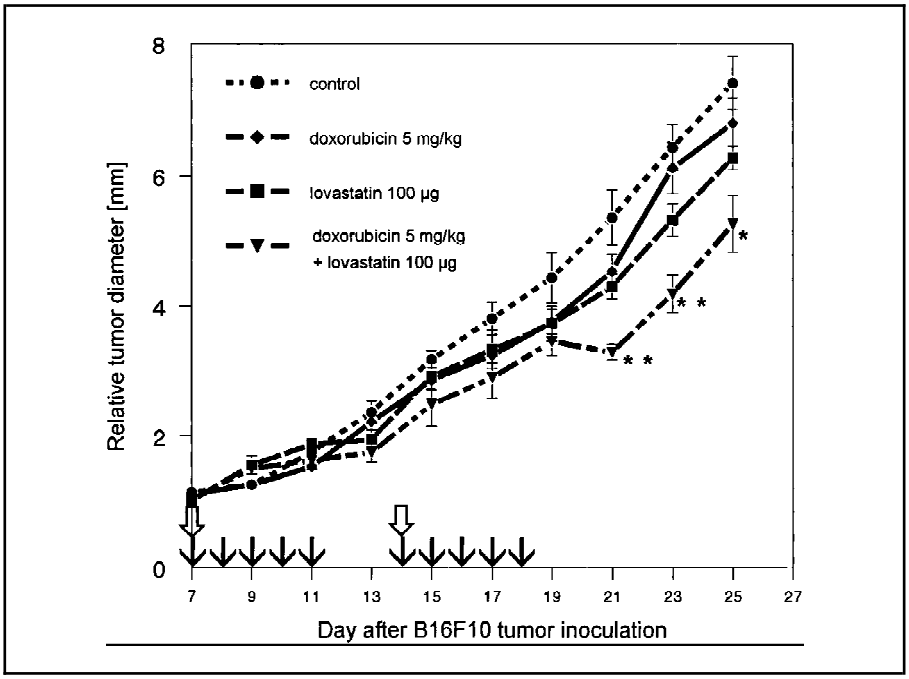

Fig. 1. Effects of treatment with doxorubicin and/or lovastatin on B16F10 tumor growth. Mice were inoculated with 1×10^6 (one million) of B16F10 melanoma cells. Measurements of tumor diameter started on day 7 after inoculation of tumor cells. Mice were injected with (↓) lovastatin (100 µg/day intratumorally on days 7–11 and on days 14–18) and/or (⇩) doxorubicin (5 mg/kg, intraperitoneally, two doses on days 7 and 14). Mean relative tumor diameter ± standard error were measured. * = $P<.05$ and ** = $P<.005$ (analysis of variance, Kruskal–Wallis test followed by a Dunn's multiple comparisons test) in comparison with control group.

lovastatin inhibited tumor growth in B16F10 murine melanoma model. However, significant retardation of tumor growth was observed in mice treated with lovastatin in combination with doxorubicin as compared with control group ($P<.05$; analysis of variance) (Fig. 1). Potentiation of antitumor activity of some chemotherapeutics by lovastatin could help to minimize their toxicity by reducing the doses necessary to achieve the antitumor effects. Although our experiments have been performed in rodent tumor models and their results do not directly translate to humans, we cannot rule out the possibility that application of statins will eventually extend to include supplementation of tumor therapy, particularly in elderly patients with coronary heart disease.

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Re: Breast Implants and Cancer

Brinton and Brown *(1)* recently reviewed the topic of breast implants and cancer. While their review was comprehensive, there are some references I feel should be added to those they cited.

Concerning sarcomas, there have been five publications *(2–6)* describing aggressive fibromatosis (desmoid), at least three of which began in the fibrous capsule around the implant. If one considers a desmoid as a slow-growing fibrosarcoma, can some of these cases be solid-state carcinogenesis in the human?

Other types of sarcomas of the breast in patients with breast implants include malignant fibrous histiocytoma and myxoid sarcoma and are described in *(7,8).*

Squamous cell carcinoma of the breast is extremely rare. There have been two cases reported recently *(9–11),* one involving the breast implant fibrous capsule and one occurring around injected silicone. These two cases are approximately 3.8% of all reported cases since 1917.

Finally, another case of lymphoma has been reported *(12).*

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Response

We thank Dr. Shiffman for noting these additional reports of cancer among patients with silicone breast implants. The goal of our review was to determine the etiologic relevance of silicone implants to subsequent cancers. Case reports must therefore be cautiously interpreted. However, as we indicated, they provide insights as to possible avenues for future research. The question of whether slow-growing fibrosarcomas should be considered as evidence of solid-state carcinogenesis is one that will not be answered by epidemiologic studies. Further resolution of the relationship of silicone implants to cancer risk should also involve laboratory approaches, some of which were discussed in our review.

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Simultaneous Production of Parathyroid Hormone-Related Protein and Granulocyte Colony-Stimulating Factor in Renal Pelvic Cancer

We treated a 53-year-old man for renal pelvic squamous cell carcinoma of the right kidney. His tumor was not totally resected because of intensive adhesion to surrounding tissue. Systemic chemotherapy and radiotherapy were not attempted because of the patient's poor general condition.

Two months after surgery, as the remaining tumor progressed, the patient exhibited hypercalcemia (corrected serum calcium level, 19.0 mg/dL) and leukocytosis (116 780/mm^3, with >90% of the leukocytes consisting of mature granulocytes), but did not have any apparent inflammatory disease or bone metastasis. Analysis of serum for levels of parathyroid hormone-related protein (PTHrP) and granulocyte colony-stimulating factor (G-CSF) indicated that elevated values of 12.0 pmol/L (normal, <1.1 pmol/L) and 202 pg/mL (normal, 6.0–21.9 pg/mL), respectively, were present. The cancer cells of surgical specimens stained positively with both anti-human PTHrP antibody and anti-human G-CSF antibody.

The patient received one course of bisphosphonate (30 mg) by intravenous infusion over 4 hours to decrease the serum calcium level; 2 weeks later, the level was within the normal range and then elevated gradually. At the same time, the white blood cell count fell to 44 700/mm^3 and elevated a few days after the corrected serum calcium level did (Fig. 1). The patient died of carcinoma 110 days postoperatively.

Bisphosphonate does not suppress the production of PTHrP but inhibits osteoclastic bone resorption and is used in treating humoral hypercalcemia of cancer. Although bisphosphonate causes transient leukopenia as a side effect 24–48 hours after the first infusion, the white blood cell count returns to the normal range a few days after dose reduction *(1,2).* In the PTHrP-producing tumors (four renal cell carcinomas and two transitional cell carcinomas), bisphosphonate reduced only the serum calcium level and decreased neither the white blood cell count nor the serum levels of PTHrP. Therefore, in this case it is unlikely that reduction of the white blood cell count is an effect of bisphosphonate.

It has been reported that the simultaneous acquisition of G-CSF production and expression of its receptor by bladder cancer cells enhance autocrine growth of the tumor *(3)* and that leukocytes or macrophages activated by G-CSF may be responsible both for the malignant transformation of normal cells and for the proliferation or metastasis of malignant cells *(4,5).* These reported results suggest that the G-CSF may be responsible for the growth of G-CSF-producing tumors.

We did not examine serum levels of PTHrP and G-CSF when the corrected serum calcium levels and the white blood cell counts decreased to the minimum values. However, it is unlikely that bisphosphonate suppresses the production of PTHrP and G-CSF antitumor effect. Furthermore, this parallel phenomenon was a one-time episode, since bisphosphonate was not injected twice.

At present, it is unclear not only whether this parallel phenomenon is calcium dependent but also how bisphosphonate modifies the mutual action between PTHrP and G-CSF. However, it might be likely that bisphosphonate in-

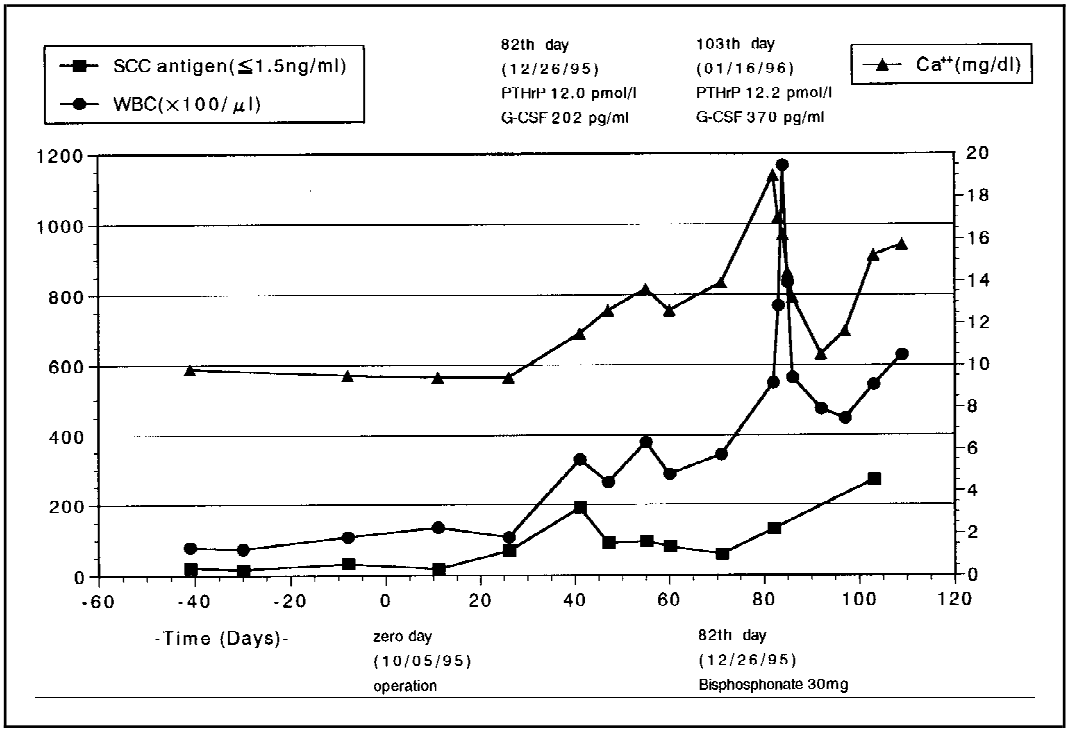

Fig. 1. Clinical values of white blood cell count, corrected serum calcium level, and squamous cell carcinoma (SCC) antigen in serum.

teracts with the other cytokines that modify the action of G-CSF. Our data may help explain the complicated cytokines network (including the association between calcium and G-CSF) in tumors that simultaneously produce PTHrP and G-CSF.

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We thank Hiroyuki Oshima for his helpful discussion.

Re: Risk of Urinary Tract Cancers Following Kidney or Ureter Stones

A Swedish record-linkage study *(1)*, based on a cohort of 61 114 patients hospitalized for kidney or ureter stones followed for up to 18 years, found a standardized incidence ratio of bladder cancer of 1.4 based on 319 cases. The association was stronger in women, but information was not available to allow for possible confounding factors. Evidence from case–control studies is still open to discussion. The odds ratios (ORs) were 2.2 in males in an earlier U.S. study *(2)*, around 1.5 in a large multicentric U.S. study *(3)*, and 1.0 in a Danish study *(4)*. Three additional case–control studies *(5–7)* found ORs between 1.2 and 1.4.

Urinary tract stones might induce chronic irritation that may lead to proliferative urothelial changes, or mechanical effect of stones on the epithelium might increase absorption and/or exposure to carcinogens in the urine, or they may be markers of chronic infections or conditions, which may, in turn, enhance bladder cancer risk. However, it remains open to discussion whether the moderate relationship observed in case–control studies reflects a causal association rather than a more accurate recall of urinary symptoms by bladder cancer cases than controls.

Therefore, we updated our analysis on the relationship between urinary tract stones and risk of bladder cancer in a case–control study carried out in Northern Italy between 1985 and 1992 *(6)*. Cases were 431 subjects (361 men and 70 women; median age, 63 years [range, 27–79 years]) with incident histologically confirmed bladder cancer. Controls were 813 subjects (638 men and 175 women; median age, 61 years [range, 23–79 years]) admitted to the same hospital for various acute conditions not related to smoking or other known or likely risk factors for bladder cancer. A total of 21 (5%) case patients and 40 (5%) of control subjects reported a history of urinary tract stones (Table 1). The multivariate OR of bladder cancer was 1.0. Separate analysis in women found a nonsignificant OR of 2.2.

Thus, this study confirms that no major association emerged between urinary tract stones and bladder cancer. If any association exists, this may be stronger in women.

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Table 1. Distribution of 431 cases of bladder cancer and 813 controls and corresponding odds ratios with 95% confidence intervals, according to history of urinary tract stones (Milan, 1985–1992)

History of stones	Bladder cancer		Control subjects		Odds ratios (95% confidence intervals)*		
	Men	Women	Men	Women	Men	Women	All
No	343	67	602	171	1†	1†	1†
Yes	18	3	36	4	1.0 (0.5–1.8)	2.2 (0.4–10.8)	1.0 (0.6–1.8)

*Estimates from multiple logistic regression equations, including terms for age, education, and smoking habit.
†Reference category.

Response

We appreciate the interest of Tavani et al. in our study and sharing their data. Their findings of a nonsignificant twofold risk of bladder cancer associated with a history of urinary tract stones among women but no association among men were inconclusive. These results illustrate the difficulties in assessing risk associated with self-reported medical histories in case–control studies, particularly in hospital-based studies in which the controls may have conditions that are related to renal stone development or diagnosis, such as increased frequency of urinalysis or pelvic x rays.

In our population-based linked-registry cohort study, the reporting of a history of renal stones was unbiased in the sense that all cohort members were hospitalized for this condition. While no information on confounding factors was available for adjustment, our results are unlikely to be confounded by smoking, the major known risk factor for bladder cancer, since there was no excess risk of lung cancer in our cohort. A more detailed discussion of the potential limitations and advantages of our study are presented in the original paper *(1)*.

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